32. The protein of claim 2, wherein said protein comprises C-terminal 14 amino acids of Ser Asn Pro Pro Val Glu Lys Leu Leu Pro Leu Ser Leu Lys.

33. An antibody against a peptide consisting of the amino acid sequence of Ser Asn Pro Pro Val Glu Lys Leu Leu Pro Leu Ser Leu Lys.

34. The partial peptide of claim 15, wherein said partial peptide consists of the amino acid sequence of SEQ ID NO:9 ~~Ser Asn Pro Pro Val Glu Lys Leu Leu Pro Leu Ser Leu Lys.~~

35. An isolated Protein ~~A protein~~ having peptidase activity towards brain APP, wherein said protein comprises an amino acid sequence of any one of SEQ ID NOS: 2 to 4 or a variant of any of SEQ ID NOS: 2 to 4 in which no more than 30 amino acids are replaced, deleted, inserted, and/or added.

REMARKS

Support for the amendment to claim 2 can be found at e.g., page 12, line 2 of the specification. Support for the amendment to claim 26 can be found in e.g., claims 24 and 25. Support for the amendment to claim 8, 9, 12 and 16 and new claims 32-34 can be found in e.g., p. 13, lines 14-17, p. 8, lines 2-3, page 34, lines 32-34.Figure 4B and in SEQ ID NOS: 2, 3, and 4. Support for new claim 35 is provided at e.g., p. 16, lines 24-26.

The Examiner states that the application contains groups of inventions (Groups I-VIII) which do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical feature. The Examiner acknowledges that the technical feature linking Groups I-VIII is that Groups I-VIII all relate to proteases that act on brain APP, but further states that Groups I-VIII do not share a special technical feature because they do not define a contribution over the prior art. The Examiner's rationale for this statement is that a

sequence disclosed by Eaton et. al. (EMBL Accession number AB011969) shows 98% sequence identity with present SEQ. ID NO:2.

In response, Applicants elect group I. The restriction requirement is traversed insofar as it may be applied to the amended claims. All of the claims (as amended where applicable) are all distinguished from the cited reference for essentially the same reason providing unity of invention.

Applicants first clarify that the sequence of EMBL Accession number AB011969 is not the same as the sequence of Eaton *et al.* The Examiner's figure of 98% sequence identity is based on a comparison of EMBL Accession number AB011969 with present SEQ ID NO:2. However, EMBL Accession number AB01196 was released by EMBL on February 2, 2000, whereas the present application has a priority date of April 30, 1999. Therefore, the sequence of EMBL Accession number AB011969 is not prior art.

The present claims are distinguished from the sequence of the cited Eaton reference as shown in Fig. 4A of the present application. The upper portion of the figure shows a protein termed prepro-brain carboxypeptidase B (HBCPB), the subject of the present application) with a protein termed CPB, which is the protein of the Eaton reference. The figure shows that HBCPB can exists a prepro protein (including signal sequence, activation peptide and mature enzyme) (SEQ ID NO:2), a pro-protein (including activation peptide and mature enzyme) (SEQ ID NO:3) and mature enzyme (SEQ ID NO:4). The figure also shows that HBCPB differs from CPB principally in that CPB contains an insert (of 37 amino acids) in the mature enzyme portion, and that HPCPB and CPB have different C-terminal tails of 14 and 40 amino acids respectively.

Attached is BLAST search comparing present SEQ ID NO:2 with the sequence of Eaton *et al.* The search found a sequence identity of 89%. (The percentage would have been even lower if the search had included the 14 and 40 amino acid C-terminal tails of SEQ ID NO:2 and CPB in the calculation.) SEQ. ID NOS:3 and 4 show the same differences from Eaton's CPB as SEQ ID NOS:2 (i.e., SEQ ID NOS:3 and 4 lack the 37 amino insert present in CPB and have a different C-terminal tail from CPB).

Because SEQ ID NOS: 3 and 4 are shorter than SEQ. ID NO:2, then the percentage sequence identity between SEQ ID NOS: 3 and 4 and Eaton's CPB is even lower.

Because Eaton's sequences shows no more than 89% identity with any of SEQ ID NOS: 2, 3 and 4, claim 2 as amended is novel with respect to Eaton's sequence. Claims 3-7 directed to DNA encoding the protein of claim 2 are distinguished for an analogous reason in that the differences in protein sequence require corresponding differences in DNA sequence. Claim 8 as amended is distinguished because the antibody is directed to the C-terminal portion of SEQ ID NO:2 which has no equivalent in Eaton's sequence. Claims 9, 10, 12, 13, 16, 17, 18, 21-23, 30, 31 and new claims 32-34 are distinguished for essentially the same reason. Claim 11 is distinguished for the same reason as claim 2 in that claim 11 requires use of the protein of claim 2. The same is true of claims 14 and 15 and claims 27-29. New 35 is distinguished in that it requires no more than 30 substitutions, deletions or insertions relative to SEQ ID NOS:2, 3, and 4 . Eaton's sequence differs from each of SEQ ID NOS:2, 3 and 4 by the insertion of a 37 amino acids in the middle and lack of 14 amino acids at the C-terminus.

The sequence differences noted above between SEQ ID NOS:2, 3 and 4 and the sequence of Eaton have important physiological consequences. Whereas Eaton's protein was isolated from human plasma, the protein defined by present SEQ ID NOS:2, 3 and 4 is expressed in human brain (see, for example, Figures 4C and 8 of the present application). The protein defined by present SEQ ID NOS:2, 3 and 4 digests beta-amyloid peptides (especially β-amyloid 1-42) and their oligomers (see Example 7 of the instant application and Appendix 2, Fig. 4). By contrast, the postulated function of HPCBP from Eaton *et al.* is antifibrinolytic activity in plasma during blood clotting (see the instant application at p. 39, lines 30-34).

Accordingly, it is submitted that the protein defined by claim 2 is novel and nonobvious with respect to Eaton's protein. For the reasons discussed above, all other claims are distinguished for essentially the same reason, and therefore should be examined together with the Group I claims.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 2 was amended as follows:

2. (Amended) A protein comprising peptidase activity towards brain APP, wherein said protein is selected from the group consisting of,

(a) a protein comprising an amino acid sequence in which one or more amino acids are replaced, deleted, inserted, and/or added to the amino acid sequence of any one of SEQ ID NOS: 2 to 4, wherein said protein has 90% or greater identity to SEQ ID NOS 2, 3, or 4;

(b) a protein encoded by a DNA that hybridizes with a DNA comprising the nucleotide sequence of SEQ ID NO: 1, wherein said protein has 90% or greater identity to SEQ ID NOS 2, 3, or 4;

(c) a protein comprising the amino acid sequence of any one of SEQ ID NOS: 2 to 4.

Claim 8 was amended as follows:

8. An antibody against the C-terminal 14 amino acids having the amino acid sequence of Ser Asn Pro Pro Val Glu Lys Leu Leu Pro Leu Ser Leu Lys of the protein of claim 2.

Claim 9 was amended as follows:

9. A partial peptide of the protein of claim 2, wherein the partial peptide comprises the C-terminal 14 amino acids having the amino acid sequence of Ser Asn Pro Pro Val Glu Lys Leu Leu Pro Leu Ser Leu Lys.

Claim 10 was amended as follows:

10. A polynucleotide [comprising at least 15 nucleotides, which hybridizes with a DNA comprising the nucleotide sequence of SEQ ID NO: 1] C-terminal 14 amino acids of SEQ ID NO:2 having the amino acid sequence of Ser Asn Pro Pro Val Glu Lys Leu Leu Pro Leu Ser Leu Lys, or its complementary strand.

Claim 11 was amended as follows:

11. A method for screening a compound that binds to the protein of claim 2, comprising the steps of:

(a) contacting a test sample with the protein or a partial peptide thereof comprising the C-terminal 14 amino acids having the amino acid sequence of Ser Asn Pro Pro Val Glu Lys Leu Leu Pro Leu Ser Leu Lys,

(b) detecting the binding activity between the test sample and the protein or the partial peptide thereof, and

(c) selecting a compound that has an activity to bind to the protein or the partial peptide thereof.

Claim 12 was amended as follows:

12. A compound that binds to the C-terminal 14 amino acids having the amino acid sequence of Ser Asn Pro Pro Val Glu Lys Leu Leu Pro Leu Ser Leu Lys of the protein of claim 2.

Claim 16 was amended as follows:

16. A compound that binds to the C-terminal 14 amino acids having the amino acid sequence of Ser Asn Pro Pro Val Glu Lys Leu Leu Pro Leu Ser Leu Lys and has [comprising the] activity to promote or inhibit peptidase activity of the protein of claim 2.

Claim 26 was amended as follows:

26. The kit [method] of claim 25, wherein said substrate is brain APP.